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HUMATIN

Paromomycin (Humatin - Parke, Davis) is a new oral antibiotic derived from a strain of Streptomyces. It is recommended by the manufacturer for bacterial diarrheas, intestinal amebiasis, hepatic coma, and preoperative suppression of intestinal flora. Humatin has a broad spectrum of antibacterial activity closely paralleling that of neomycin. It exhibits cross-resistance in vitro with neomycin and also with streptomycin. As with neomycin, there is little absorption of the antibiotic from the intestinal tract, and little or none of the antibiotic appears in the blood or the urine. A high percentage is recovered from the feces.

At this point, there is no reason to believe that Humatin is superior to neomycin for bacterial infections of the gastrointestinal tract, for preoperative suppression of intestinal flora, or for suppression of nitrogen-forming bacteria in the gastrointestinal tract in patients with hepatic coma. Both are effective against such common enteric bacteria as Escherichia coli, Aerobacter aerogenes, B. proteus, Pseudomonas aeruginosa (B. pyocyaneus), Klebsiella pneumoniae (B. Friedlander's), Salmonella, and Shigella, as well as against Staphylococcus aureus. Humatin appears to be no more effective in the Salmonella carrier than the older drugs, such as Chloromycetin, Furoxone and neomycin.

AMEBIC INFECTIONS - Humatin is claimed to be especially useful for intestinal amebic infections, but there is no lack of effective agents for the treatment of this condition. Medical Letter consultants consider diiodohydroxyquin, USP (Diodoquin - Searle) preferable for mild or asymptomatic amebiasis. Diodoquin is effective, relatively free of side effects and less expensive. For severe amebic dysentery, present evidence does not justify the substitution of Humatin for the highly effective combination of emetine, USP and a tetracycline.

Humatin, like neomycin, shows a very low degree of toxicity when given orally; the only side effects of oral dosage so far reported are diarrhea and overgrowth of resistant organisms, particularly Monilia. Animal experiments have shown, however, that parenteral administration can cause severe liver damage. This toxicity precludes its use for amebic hepatitis and liver abscess. For these amebic infections emetine remains the drug of choice, with chloroquine (Aralen - Winthrop) as an adjunct. (For a discussion by H. Most of the treatment of amebiasis, see "Current Concepts in Therapy," N. E. J. Med., 262:513, 1960.)

In summary, clinical experience thus far with Humatin shows that this antibiotic is effective against many organisms, but it fails to demonstrate any superiority over other well-tried antibacterial and antiamebic preparations which have had the important advantage of extensive use.

Humatin is available in 250-mg. capsules at a cost of about $1 per capsule. The recommended adult dosage for amebiasis ranges from 750 mg. to 1500 mg. per day for five days. Larger doses are recommended for other infections.

NEW AND OLD ERGOTAMINE DRUGS FOR MIGRAINE

ERGOMAR AND MEDIHALER-ERGOTAMINE - Ergomar (Nordson), a soluble sublingual tablet, and Medihaler-Ergotamine (Riker), an oral inhalant, are two new ergotamine preparations offered for the relief of migraine. Theoretically these new forms of ergotamine should give more prompt and more reliable absorption of the drug than oral tablets and provide more reliable relief of migraine. Both preparations are, in fact, claimed to be as reliable as injections of ergotamine.

Although present evidence supporting the claims is very limited, and there is some disagreement among experts consulted by The Medical Letter, sublingual and inhalant ergotamine drugs do appear to be more effective than oral forms for some patients. The experience of headache clinics does not show, however, that Ergomar and Medihaler-Ergotamine are as reliable as either parenteral or rectal ergotamine preparations.

Because of poor or irregular absorption from the gastrointestinal tract, many patients have found oral ergotamine tablets disappointing, even in doses as high as 6 mg. Such patients, particularly if they dislike the inconvenience of parenteral and rectal forms, might well try sublingual or inhalant ergotamines (though some patients find the taste objectionable). All of the other forms are, of course, preferable to the oral for patients with nausea and vomiting. With all ergotamine preparations, the earlier the drug is taken during the attack, the smaller the dose that is likely to be effective, and the fewer the side effects. With all preparations, trial is needed to arrive at dosages which will be effective without acute toxic effects such as vomiting, paresthesias, leg cramps and abdominal pain.

PROPHYLACTIC USE - Clinicians are divided as to whether ergotamine preparations should be used for prophylactic purposes. Some believe such use is generally ineffective in preventing migraine attacks, and that continued or frequent ergotamine therapy can cause prolonged vasoconstriction, with the consequent risk of thrombosis and gangrene. Other clinicians believe that in the absence of vascular disease, occasional prophylactic use of ergotamine is effective and safe for many patients. Medical Letter consultants feel that a cautious prophylactic trial of ergotamine may be worthwhile with patients whose attacks are predictable and likely to be severe.

All ergotamine preparations should be used with caution, if at all, in elderly persons, and they should never be used in the presence of occlusive or spastic

vascular disease, during pregnancy, or in the presence of severe hepatic or renal disease. Dihydroergotamine has been recommended as a safer drug than ergotamine, particularly during pregnancy, but if used in equivalent therapeutic dosage (about 50 per cent higher than the dosage of ergotamine) it is probably no less toxic or freer of side effects. To minimize the risk of toxic effects with any form of ergotamine, it is generally considered advisable to give the maximum effective dose not more often than once a week.

AVAILABLE FORMS - Ergotamine preparations, oral and suppository, are available in various combinations with caffeine, analgesics, belladonna alkaloids, antihistamines, and sedatives. Perhaps the most widely sold preparation is Cafergot tablets (Sandoz), containing 1 mg. of ergotamine tartrate plus 100 mg. of caffeine. Cafergot suppositories contain 2 mg. of ergotamine tartrate plus 100 mg. of caffeine. Cafergot P-B tablets and suppositories contain, in addition, a barbiturate and bellafoline, the latter presumably to control gastrointestinal spasm in migraine. Gynergen tablets and ampules (Sandoz) contain only ergotamine tartrate. Ergomar (sold in packages of twelve 2-mg. tablets) contains only ergotamine tartrate, as does Medihaler-Ergotamine (which costs about $8.50 and delivers over fifty 0.36-mg. doses).

While clinical impressions support the use of caffeine and other drugs in combination with ergotamine in the treatment of migraine, adequately controlled trials showing the superiority of such combinations over simple ergotamine are lacking. A sedative may sometimes be useful in migraine therapy, but it will usually be preferable for the doctor to prescribe the sedative separately, with the amount and timing suited to the individual patient.

The following table shows the different dosage forms in estimated order of effectiveness, though many patients can get adequate relief with any one of the forms.

Estimated Order of Effectiveness	Recommended Range of Doses	Approximate Cost of Minimum Dose
Parenteral	0.25 to 0.5 mg.	85¢ (Gynergen ampules)
Suppository	2 mg. to 4 mg.	60¢ (Cafergot)
Inhalant	0.36 mg. to 2.16 mg.	17¢ (Medihaler)
Sublingual	2 mg. to 6 mg.	45¢ (Ergomar)
Oral	2 mg. to 6 mg.	40¢ (Cafergot)

Ergotamine tartrate injection, USP (0.25-mg. ampules), ergotamine tartrate tablets, USP, and ergotamine tartrate and caffeine tablets are available from a number of companies under the generic names and at lower prices.

ACTH VERSUS CORTICOSTEROIDS

With a variety of corticosteroids now available in parenteral form, the question often arises as to the relative merit of these preparations and of ACTH. Injections of ACTH have been considered as a more "physiological" means of in-

ducing hyperadrenalism, since ACTH stimulates the adrenal cortex to secrete an entire spectrum of hormones whereas injections of corticosteroids provide only one component of the spectrum. The advantage, if any, appears to have no clinical significance. On the contrary, ACTH has a disadvantage imposed by the limited secretory capacity of the adrenal cortex; beyond a certain dosage, additional ACTH has no effect. With corticosteroids, there is no such limitation.

In the United States, ACTH is seldom used for prolonged treatment, partly because of the undesirability of frequent injections, and partly because retention of sodium and water (with resulting hypertension) and excessive androgenic action (with resulting hirsutism) are much more marked with ACTH than with most corticosteroids.

ADRENAL ATROPHY - One advantage claimed for ACTH over corticosteroids in prolonged use is a reduced incidence of adrenal cortical atrophy. To avoid this risk during prolonged corticosteroid therapy, some clinicians recommend the substitution of ACTH in doses of about 40 units for one to four days at intervals of one month. Lasting adrenal atrophy or unresponsiveness is quite rare, however (R. M. Salassa, et al., JAMA, 152: 1509, 1953). Furthermore, authorities differ as to whether the periodic substitution of ACTH for corticosteroids does prevent it.

In Addisonian crises and in surgical extirpation of the adrenal cortex, only the corticosteroids can, of course, be employed. The one undisputed use for ACTH is in diagnostic tests for the competency of the adrenal cortex; in the presence of adrenal insufficiency, the administration of ACTH will not result in a rise in either plasma or urinary corticosteroids. Oral corticosteroids can be used in most instances in which rapid corticosteroid effects are desired; they are absorbed and become effective in a few hours.

HYPERSENSITIVITY REACTIONS - The availability of fast-acting and potent parenteral corticosteroids should not cause physicians to neglect epinephrine hydrochloride, USP as the first drug to be used for the immediate relief of acute anaphylactic reactions. For other hypersensitivity reactions such as urticaria and angioneurotic edema, either oral or parenteral antihistamines are often fully effective. When epinephrine and antihistamines fail, oral corticosteroids should be tried. Either parenteral steroids or ACTH may have special usefulness (as in relief of status asthmaticus and severe acute allergic dermatoses) when oral steroids cannot be ingested or absorbed or when more rapid response is required.

The average duration of effect of aqueous intravenous or intramuscular solutions of ACTH is about six hours; of repository gels, 24 hours; of Cortrophin-Zinc (Organon), 48 hours. Preparations of cortisone, hydrocortisone, prednisolone, methylprednisolone and dexamethasone are available for intramuscular and intravenous use. The succinate and phosphate esters of various corticosteroids may be used either intravenously or intramuscularly; they are quickly effective and act over a period of approximately four to six hours. Acetates of the various steroids are available as suspensions for intramuscular use; because of their very low solubility they are slower to take effect, but the effects are prolonged, lasting from two to 14 days.

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